Remarks

The Office Action dated December 4, 2008 has been carefully reviewed and the following comments are made in response thereto. In view of the following remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Without prejudice or disclaimer and for the sole purpose of advancing prosecution, Applicant has canceled the currently pending claims. Claims 17 to 23 are similar to claims 7 and 9 to 14 with the exception that these claims recite a herpes simplex virus instead of a recombinant HSV. Exemplary support for this amendment is found on page 8, lines 21 to 26 of the specification. New claims 22 and 23 further specify the routes of administration (*see e.g.* page 4, lines 17-23, page 4, lines 3-12, page 11, lines 3-10, Example 3 (page 20, line 21 to page 21, line 30) and Example 8 (page 25, line 5 to page 27, line 12) of the specification). Claims 26 and 27 encompass the subject matter of previous claims 15 and 16. No new matter has been added.

The Rejection under 35 U.S.C. 102(b) should be withdrawn

Claims 7, 9, 12 to 14 were rejected under 35 U.S.C. 102(b) as allegedly being anticipated by Coffin. Applicant respectfully disagrees. While Applicant has canceled the previously pending claims and thereby rendered the rejection moot, the new claims encompass similar subject matter. The references cited by the Examiner neither anticipates nor renders the pending claims obvious.

The present invention relates to a novel method treatment of cancer which enhances existing oncolytic virus therapy. Oncolytic virus therapy, also called tumor-killing virus therapy, refers to a therapy in which cancer cells are infected with a herpes simplex virus (HSV), which selectively replicates only within cancer cells, is incapable of replicating in normal cells and does not damage normal tissue (*see* page 1, line 24 to page 2, line 4 of the specification). The virus replicates *in situ* after infecting the cancer cells and the infected cancer cells are destroyed by direct oncolytic activity of the virus, while normal tissue is not affected. Any HSV that selectively replicates in the cancer cells can be used to enhance the effect of oncolytic virus therapy according to the method of the present invention, whether or not the HSV has been genetically modified, or alternatively, whether or not the HSV can express proteins encoded by the genes useful for anticancer activities (including genes encoding cytokines and interleukins). To enhance the effect of oncolytic virus therapy, however, it is necessary to administer such an HSV together with interleukin 18 as a protein (*i.e.* not as a protein encoded by the HSV). In addition, it should be noted that, for the claimed methods, the amount of interleukin 18 co-administered as

a protein can be so low that the administration of interleukin 18 alone results in little anti-cancer activity (*i.e.* there is almost no anti-cancer effect). Applicant discovered that interleukin 18 as a protein at such low amounts was sufficient to enhance the efficacy of oncolytic virus therapy when co-administered with a herpes simplex virus that selectively replicates within cancer cells.

The pending claims are clearly not anticipated by Coffin. Unlike the claimed invention, Coffin discloses construction of recombinant HSV which may contain a gene encoding immunomodulatory protein such as cytokine and is replication competent in tumor cells (*see* claim 1 of Coffin). The constituents of the virus itself disclosed in Coffin are important, since the anticancer effect is increased by and caused by the immunomodulatory protein itself expressed in the cancer cells. In contrast for the claimed invention, it is important to co-administer the HSV that selectively replicates within the cancer cells and interleukin 18 as a protein, whether or not the HSV has been genetically modified to express genes useful for an anticancer activity. Coffin does not disclose or suggest such co-administration of HSV and a cytokine protein, in particular co-administration of HSV virus with interleukin 18 as a protein as required by the claims. Also, Coffin does not disclose or suggest any method for enhancing the effect of oncolytic virus therapy. Any of concept, approach, and mechanism for the method of the present invention is largely different from the disclosure.

As the Examiner noted Coffin discloses a recombinant HSV which may *express* a cytokine. Coffin however clearly does not specifically enumerate interleukin 18. The pending claims require co-administration of HSV with interleukin 18 protein. There is a clear difference between (1) co-administration of a virus and a protein (interleukin 18) as claimed and (2) administration of a virus which *may* express a certain protein (such as *e.g.* interleukin 18). In the former case, interleukin 18 is able to assert its effects immediately, while in the latter case, the protein is not available until protein is expressed and exported out of the cell. Coffin also fails to disclose or suggest that two different cytokines may be co-administered. Coffin further does not disclose or suggest that interleukin 18 protein is administered systemically or that interleukin 12 protein is administered locally. There is no teaching, suggestion or other extrinsic evidence that suggests that Coffin discloses administration of a recombinant HSV with co-administration of interleukin 18 protein and interleukin 12 protein and (3) co-administration of interleukin 18 protein and a recombinant herpes simplex virus that expresses interleukin 12 protein. The mere disclosure of expression of a cytokine by a recombinant virus does not disclose or suggest co-administration of a recombinant virus and a specific enumerated cytokine.

As the Examiner is aware, for the disclosure of a genus (*e.g.* a cytokine) to anticipate a species (*e.g.* interleukin 18), the prior art needs to spell out a definite and limited class of compounds that enables

one of skill in the art to at once envisage each member of this limited class (*see Eli Lily & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369, 1376 (Fed Cir. 2006)). At the time of the invention, many cytokines with many different functions and signaling pathways were known. Thus the term "cytokine" as disclosed by Coffin encompasses a large group of chemicals that do not share the common characteristic feature of enhancing the effect of oncolytic virus therapy. Thus, one skilled in the art could not recognize which cytokine could enhance the effect of oncolytic virus therapy, despite the disclosure of Coffin. Accordingly, Coffin does not inherently disclose the specific claimed cytokines.

In light of the foregoing amendments and remarks, Applicant respectfully submits that the pending claims are not anticipated by Coffin.

The Rejections under 35 U.S.C. 103(a) should be withdrawn

Claims 7, 9 to 16 are rejected as allegedly being obvious over Johnson *et al.* and Yamanaka *et al.* Applicant respectfully disagrees. While Applicant has canceled the previously pending claims and thereby rendered the rejection moot, the new claims encompass similar subject matter. All of the pending claims require co-administration of interleukin 18 protein and HSV, which replicates selectively in cancer cells. The virus may have deletions or inactivation in the genome and may express interleukin 12. All of the pending claims are clearly not obvious over the combination of the references cited by the Examiner.

Similar to Coffin, Johnson *et al.* discloses a modified HSV, which may encode a therapeutic product (*e.g.* a cytokine) and which may used for *e.g.* the treatment of cancer (*see* claims 1 to 5 and claims 33 to 34). The constituents of the HSV itself are important to achieve a good anticancer effect following the expression of the therapeutic product (*e.g.* a cytokine). Johnson *et al.* fails to disclose or suggest any method for enhancing the effect of the oncolytic virus therapy or co-administration of the herpes simplex virus and interleukin 18 protein.

Yamanaka *et al.* shows that an effect of immune therapy provided by interleukin 12-secretory cells (*i.e.* MBT2 cells which was transfected with a gene encoding interleukin 12) was increased by a systematic administration of interleukin 18 (*see e.g.* Abstract). However, the Yamanaka *et al.* article does not describe or suggest any virus or any method for enhancing the effect of oncolytic virus therapy. Yamanaka *et al.* emphasizes the synergic anti-cancer effect obtained by the interaction between interleukin 18 and interleukin 12, while the enhancing effect of interleukin 18 on oncolytic virus therapy does not depend on the interaction between interleukin 18 and interleukin 12.

Those of skill in the art would not have been motivated to combine the references as suggested by the Examiner. On the contrary, at the time of the invention, the state of the art taught away from making

such a combination. At the time of the invention, it was known that interleukin 18 inhibits HSV infection (*see* Fujioka *et al.* at Abstract (copy attached)). Specifically, Fujioka *et al.* showed that interleukin 18 is involved in innate immunity against herpes simplex virus infection in mice. As the Examiner may be aware, innate immunity refers to an immune response which is first caused in host cells upon viral infection and therefore provides for an inhibition of the viral infection. The experimental results by Fujioka *et al.* demonstrate HSV infection was actually inhibited when interleukin 18 was administered (see *e.g.* page 2402, right column, lines 1 to 22 and page 2407, left column, lines 2 to 10). Since the inhibition of the viral infection should reduce or lower the tumor-killing effect caused by a herpes simplex virus, a person skilled in the art would expect that the administration of interleukin 18 would reduce or lower the tumor-killing effect caused by a herpes simplex virus (*i.e.* reduce or lower the effect of oncolytic virus therapy). Accordingly, one of skill in the art faced with the problem of enhancing oncolytic virus therapy would not have been motivated to co-administer interleukin 18 with a herpes simplex virus that selectively replicates in tumor tissue. At the time of the invention, conventional wisdom in the art (as evidenced by Fujioka *et al.*) taught away from the co-administration of HSV and interleukin 18 as a protein and also taught away from achieving the observed enhanced effect on oncolytic virus therapy (*see* M.P.E.P. 2141.02 (obviousness cannot be predicated on what is not known at the time an invention was made)).

However, contrary to what was known at the time of the invention, Applicant demonstrated that the viral replication capacity of a recombinant herpes simplex virus is not affected by co-administration of interleukin 18. Specifically, the Applicant surprisingly discovered that the tumor-killing effect caused by a HSV, which selectively replicates in cancer cells, was unexpectedly enhanced by the administration of interleukin 18 as a protein even at low amounts. Examples 1 and 3 clearly illustrate that the interleukin 18 protein enhances the anti-cancer efficacy of G47Δ (*see* page 18, line 21 to page 20, line 3 and page 20, line 21 to page 21, line 20 as well as Figures 1 and 3 of the specification). Since G47Δ had not been modified to express a gene encoding a cytokine, it is apparent that this effect was obtained by administration of the interleukin 18 protein and not by the gene expression of the cytokine. In addition, Example 8 shows the enhancing effect of administration of interleukin 18 protein in oncolytic virus therapy utilizing "T-mfIL12", which is a herpes simplex virus containing the gene encoding mouse interleukin 12 (*see* page 25, line 4 to page 27, line 11 of the specification). When T-mfIL12 was injected into the tumor tissue and interleukin 18 was systemically administered as (*see* Figure 9 (Mock +IL-18)), the growth of the tumor that was located remotely from the tumor tissue injected with the T-mfIL12 was significantly inhibited (*see* Figure 9 (T-mfIL12+Mock and T-mfIL12+IL-18)), showing the systemic

enhancement effect of interleukin 18 on oncolytic virus therapy even at low doses. Similar to the results of Examples 1 and 3, the enhancement effect shown in Example 8 was obtained by the interaction between the virus and interleukin 18. The surprising results clearly indicate that the pending claims are not obvious.

In light of the foregoing amendments and remarks, Applicant respectfully submits that the pending claims are not obvious over the combination of any of the references cited by the Examiner.

Conclusion

It is respectfully submitted that all claims are now in condition for allowance, early notice of which would be appreciated. Should the Examiner disagree, Applicant respectfully requests a telephonic or in-person interview with the undersigned attorney to discuss any remaining issues and to expedite the eventual allowance of the claims.

Except for issue fees payable under 37 C.F.R. 1.18, the Commissioner is hereby authorized by this paper to charge any necessary fees during the entire pendency of this application including fees due under 37 C.F.R. 1.16 and 1.17, which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310.

Respectfully submitted,
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